Theoretical Analysis of the Heterocyclic [4+2] Cycloaddition Between Pyridinium Ion and Enol Ether

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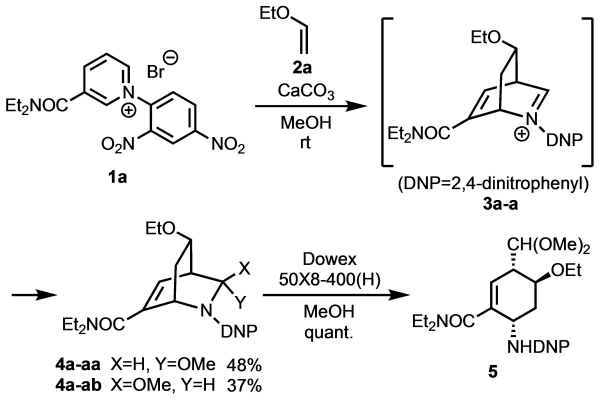
Dearomative heterocyclic [4+2] cycloaddition between the *N*-(2,4-dinitrophenyl)pyridinium ion of nicotinamide and an enol ether was analyzed by Density Functional Theory (DFT) calculations. The calculation revealed that the reaction undergoes stepwise bond formation rather than occurring in a concerted manner. The experimental products were found to be both kinetically and thermodynamically favored. The calculated transition states and intermediate suggested that the high diastereoselectivity is derived from the electrostatic interaction between the 2-nitro group of the pyridinium ion and the hydrogen of the enol ether.



Scheme 1. [4+2] Cycloaddition of *N*-(2,4-dinitrophenyl)pyridinium ion of nicotinamide with enol ether.[7]

The dearomatization reaction has been studied extensively since it is a very attractive method to construct complex functionalized molecules.[1] As a recent example, photochemical [4+2] cycloaddition of benzene with triazolinedione and the following transformation were proven to be a very effective approach to synthesize poly-functionalized cyclohexane derivatives.[2] In this study, DFT analysis was utilized for the development of the reaction.[2b] Dearomative [4+2] cycloaddition of pyridine derivatives with alkenes could also be an attractive approach for syntheses of poly-functionalized aminocyclohexane derivatives. However, whereas [4+2] cycloadditions of 1,2-dihydropyridine,[3] 2-pyridone,[4] and isoquinolines[5] have been developed as useful methods, the reaction of pyridines was limited to just a few examples of special substituted pyridines.[6,7] One of the pioneering works of [4+2] cycloaddition of pyridines was reported by Falck *et al.* in 1990.[7] They developed an inverse electron-demand [4+2] cycloaddition between *N*-(2,4-dinitrophenyl)pyridinium ion **1a** of nicotinamide and enol ether **2a** to generate **3a-a** followed by the addition of methoxide ion to give **4a-aa**. Subsequent ring-opening afforded a poly-functionalized aminocyclohexene **5** (Scheme 1). Owing to the high yield, the high diastereoselectivity, and very mild reaction conditions, we believe that this conversion could be a good starting point to develop general and useful inverse electron-demand [4+2] cycloaddition reactions of pyridine derivatives to synthesize poly-functionalized aminocyclohexane derivatives. Concerning the reaction mechanism, a stepwise formation of two bonds involving an intermediate with one bond was proposed for the [4+2] cycloaddition between related isoquinolinium ions and enol ethers rather than a concerted mechanism by the analysis of the reaction kinetics and the products.[5] However, [4+2] cycloadditions of these pyridinium or isoquinolinium ions have not been theoretically studied to date. In order to elucidate the reaction mechanism of the inverse electron-demand [4+2] cycloaddition of the pyridinium ion as well as the origin of the high diastereoselectivity toward the application and development of related reactions, we elucidated the reaction mechanism of the [4+2] cycloaddition of the pyridinium ion of nicotinamide and the enol ether by DFT calculations.

The calculation was conducted at the B3LYP/6-31G(d) level of theory using the Gaussian 16 and Reaction plus Express program packages.[8,9] To reduce the number of possible conformations, ethoxy groups of **1a** and **2a** were replaced by methoxy groups in model compounds **1b** and **2b** for the calculation (Scheme 2). Experimentally, the reaction of **1a** and **2a** afforded the intermediate **3a-a** among the two possible diastereomers, and the subsequent addition of methoxide gave a mixture of two diastereomers **4a-aa** and **4a-ab** among the four possible diastereomers. In the DFT calculations, the thermodynamic stability of two diastereomers **3b-a** and **3b-b** was first investigated. The diastereomers **3b-a** and **3b-b** each have two conformers **3b-a1**, **-a2** and **3b-b1**, **-b2** derived from the direction of the DNP group (Scheme 2, Figure 1). The calculation of the four structures indicated that **3b-a2**

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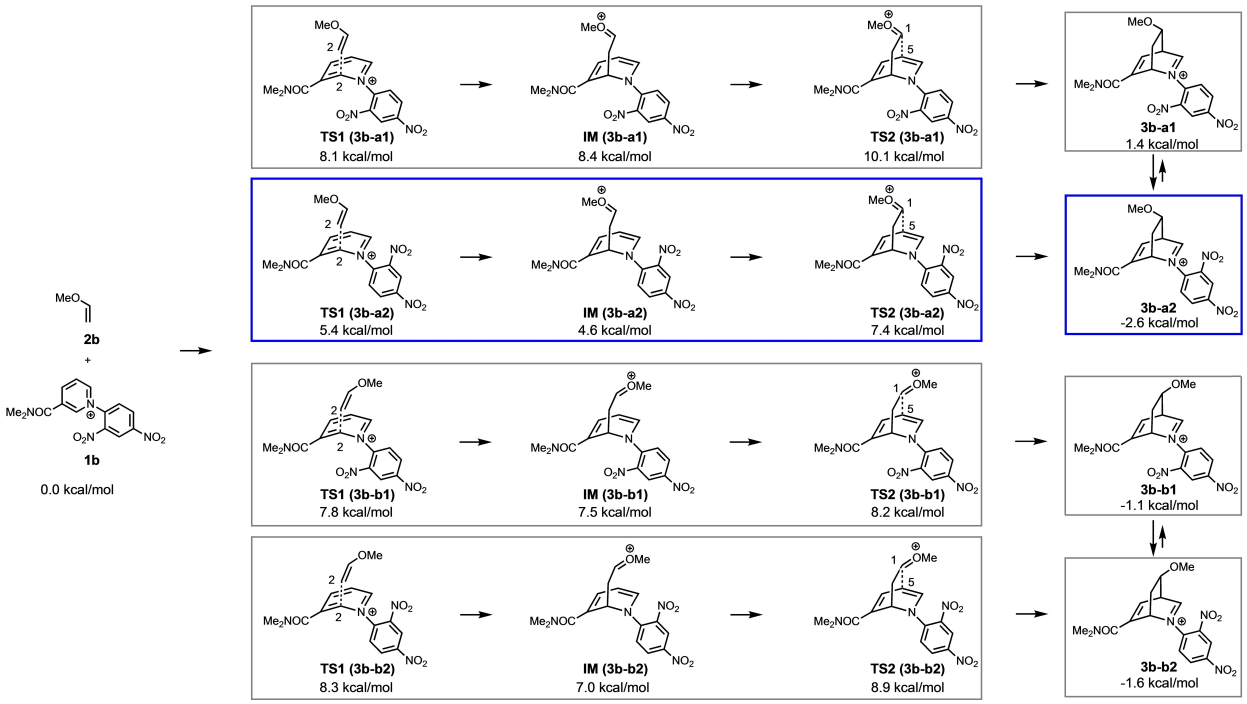

Scheme 2. Calculated reaction pathways and energies [B3LYP/6-31G(d)] of [4 + 2] cycloaddition of **1 b** and **2 b** to **3 b**. The energies are based on **1 b** and **2 b**.

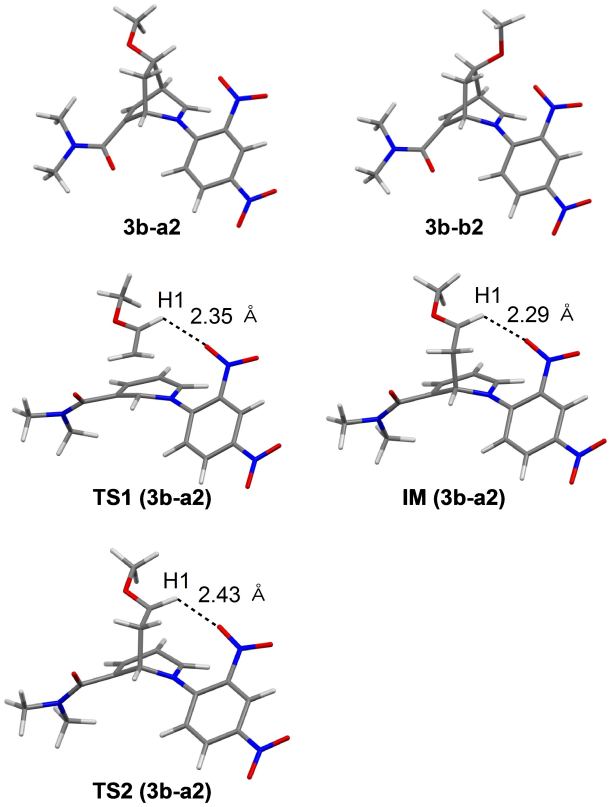

Figure 1. Calculated structures of intermediates and transition states.

(−2.6 kcal/mol) and **3 b-b2** (−1.6 kcal/mol) were the more stable conformers in each pair, with lower energies than the sum of the starting materials **1 b** and **2 b**. Among the two diastereomers, **3 b-a2** was more stable than **3 b-b2**. The stereochemistry of the thermodynamically favored **3 b-a2** in the calculation agreed with that of the experimental intermediate **3 a-a**.

Next, the reaction mechanism of the [4 + 2] cycloaddition of **1 b** and **2 b** to **3 b** was investigated. Depending on the directions of the MeO and DNP groups, four pathways to **3 b-a1**, **-a2** and **3 b-b1**, **-b2** were calculated (Scheme 2, Figure 1). In every pathway, stepwise bond formation through two transition states (**TS1**, **TS2**) and an intermediate (**IM**) was found.[10] The first transition state with a smaller activation energy is the rate-determining step, and the pathway through **TS1 (3 b-a2)** (5.4 kcal/mol), **IM (3 b-a2)** (4.6 kcal/mol), and **TS2 (3 b-a2)** (7.4 kcal/mol) to **3 b-a2** (−2.6 kcal/mol) has the lowest energy in every step among the four pathways. From these results, the formation of **3 b-a2** is not only thermodynamically but also kinetically favored. From the calculated energies, it is noteworthy that the energies of **TS1 (3 b-a2)** (5.4 kcal/mol) and **IM (3 b-a2)** (4.6 kcal/mol) were significantly lower than those of the transition states and the intermediates in the other three pathways. From the analysis of the calculated structures, we found that the distances (2.35 and 2.29 Å) between the oxygen atom of the 2-nitro group and the H1 atom at the α-position of the MeO group are significantly shorter than the sum (2.72 Å) of the van der Waals radii of the oxygen and hydrogen atoms (Figure 1). The short distances suggest an electrostatic interaction between the atoms, which stabilizes the transition states and the intermediate. The 2-nitro group provides the attractive force in the pathway rather than steric repulsion.

Finally, the products **4 b-aa** and **4 b-ab** formed by the addition of methoxide ion to **3 b-a** were calculated (Figure 2).

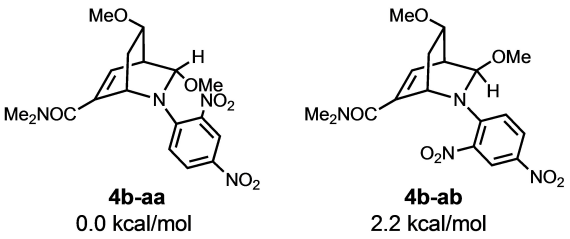

Figure 2. Calculated energies of **4b-aa** and **4b-ab**. The energies are based on **4b-aa**.

The diastereomer **4b-aa** (0.0 kcal/mol) was thermodynamically favored over **4b-ab** (2.2 kcal/mol), which agreed with the stereochemistry of the experimental major product **4a-aa**.

In conclusion, DFT calculations revealed the stepwise reaction mechanism of the inverse electron-demand [4+2] cycloaddition of a pyridinium ion with an enol ether. Experimental products were found to be both the kinetically and thermodynamically favored diastereomers. The analysis suggested that the electrostatic interaction between the 2-nitro group of the 2,4-dinitrophenyl group and the enol ether significantly stabilizes the favored transition state and intermediate, resulting in the high diasteroselectivity. The validity of the theoretical analysis of the reaction mechanism was well-demonstrated in this study. We believe that this theoretical analysis will lead to the design of dearomative [4+2] cycloadditions of pyridine derivatives for the syntheses of polyfunctionalized aminocyclohexane derivatives.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: [4+2] cycloaddition · density functional theory · pyridinium · reaction mechanism · stepwise

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